IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.	:	09/653,794	Confirmation No. 5973
Applicant	:	Meir S. Sacks et al.	
Filed	:	September 1, 2000	
Title:	:	COMPOSITIONS AND METHODS FOR TREATING SEXUAL DYSFUNCTION	
TC/A.U.	:	1615	
Examiner	:	Gollamudi S. Kishore	
Docket No.	:	286262-00005	
Customer No.	:	29694	

APPEAL BRIEF

Mail Stop Appeal Brief – Patents
Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

June 28, 2005

Sir:

Appellants hereby appeal the final rejection of this application set forth in the Office Action dated November 1, 2004.

REAL PARTY IN INTEREST

The real party in interest is Meir S. Sacks, the assignee of the captioned application.

RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences that are believed to directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

STATUS OF CLAIMS

Claims 13, 18, 19 and 21-25 are pending in the application.

Claims 13, 18, 19 and 21-25 stand rejected under 35 U.S.C. § 103(a).

Claims 13, 18, 19 and 21-25 are appealed. A listing of the appealed claims is provided in the Appendix.

STATUS OF AMENDMENTS

There are no outstanding amendments.

SUMMARY OF THE INVENTION

The present invention provides a method for treating sexual dysfunction in a female patient comprising topically administering to the genitals of said patient an effective amount of esterified L-arginine comprising ethyl ester of L-arginine and an effective amount of an antioxidant (page 3, lines 17-20; page 3, line 30 to page 4, line 3; page 4, lines 19-22; and page 5, line 17).

ISSUES

1. Whether Claims 13, 18, 19 and 21-25 are properly rejected under 35 U.S.C. § 103(a) as being unpatentable over Fossel '713 or Wallace '037 in view of Chobanian et al. '847.

2. Whether Claims 13, 18, 19 and 21-25 are properly rejected under 35 U.S.C. § 103(a) as being unpatentable over Fossel '713 or Wallace '037 in view of Chobanian et al. '847, and further in view of Duckett et al. '824 by itself or in further combination with Wysor '002.

GROUPING OF CLAIMS

Claims 13, 18, 19 and 21-25 stand or fall together.

ARGUMENT

The 35 U.S.C. § 103(a) Rejections are Improper and Should Be Reversed

Independent Claim 13 recites a method for treating sexual dysfunction in a female patient comprising topically administering to the genitals of said patient an effective amount of esterified L-arginine comprising ethyl ester of L-arginine and an effective amount of an antioxidant. Appellants have unexpectedly found that topically applied compositions comprising ethyl ester of L-arginine are highly effective in treating female sexual dysfunction.

Independent Claim 13 was rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 6,207,713 to Fossel or U.S. Patent No. 6,476,037 to Wallace in view of U.S. Patent No. 6,139,847 to Chobanian et al. The Office Action states that:

> Fossel discloses topical delivery of L-arginine (nitric oxide inducer and vasodilator) or the treatment of erectile dysfunction (note abstract, Example 3 and claims).
>
> Similarly, Wallace discloses the topical administration of L-arginine for the treatment of erectile dysfunction (abstract, col. 15, line 53 et seq., Examples and claims).
>
> Chobanian et al. while disclosing a treatment of fibrosis teach that antioxidants such as ascorbate, tocopherol and beta-carotene are NO catabolism inhibitors and advocates the use of the combination of NO stimulators (L-arginine) and NO catabolism inhibitors (note the abstract, col. 3, line 6 through col. 4, line 67, col. 5, line 40, Example 1 and claims). Chobanian further teaches the knowledge in the art of the use of NO donors for the treatment of conditions including impotence (col. 3, lines 6-10).
>
> The inclusion of an antioxidant in the L-arginine containing compositions of Fossel or Wallace for the treatment of erectile dysfunction would have been obvious to one of ordinary skill in the art, with the expectation of obtaining at least an additive effect, since Chobanian teaches that antioxidants are NO catabolism inhibitors and that they could be used in combination with NO stimulators. Although neither Fossel nor Wallace teach the use of the composition for female sexual dysfunction by topical application to the clitoris, it would have been obvious to one of ordinary skill in the art to use the composition for females with a reasonable expectation of success since the clitoris is supplied with blood vessels and the principle of vasodilatation is the same.

Independent Claim 13 was further rejected under 35 U.S.C. § 103(a) as being unpatentable over the Fossel '713 or Wallace '037 in view of Chobanian et al. '847, and further in view of U.S. Patent No. 6,007,824 to Duckett et al. by itself or in further combination with U.S. Patent No. 6,031,002 to Wysor. The Office Action states that:

> Duckett et al as discussed before, disclose compositions containing L-arginine and ginseng (antioxidant) for the treatment female sexual dysfunction. Duckett et al teach that the sexual stimulation causes local release of NO resulting in the smooth muscle relaxation and the increased

blood flow. They further teach that L-arginine releases NO resulting in smooth muscle relaxation and increased inflow of blood (note the abstract, col. 1, line 12 through col. 2, line 46, col. 3, line 65 through col. 4, line 50 and claims). The mode of administration in Duckett however, is oral and not topical.

Wysor as discussed before, while disclosing prostaglandin (vasodilator) formulations for enhancing female sexual response teaches that the formulations can be applied topically to the genitals and such a topical treatment is highly effective. Wysor further teaches the use of liposome formulations for the delivery of the composition (note the abstract, columns 1-3 and claims).

In essence, the reference of Duckett shows that the principle of NO release and the increased blood flow in females by the vasodilator, arginine and that of Wysor shows that a vasodilator can be applied topically the genitals to treat female sexual dysfunction.

One of ordinary skill in the art would be motivated further to use the composition of arginine and the antioxidants of Fossel, Wallace and Chobanian to treat the female dysfunction since the effectiveness of arginine against female dysfunction and that of Wysor shows that a vasodilator composition can be applied topically to the female genitals to achieve the desired goal.

Claim 13 distinguishes over the prior art of record. None of the applied references alone, or in combination, disclose a method for treating sexual dysfunction in a female patient in which an effective amount of esterified L-arginine comprising ethyl ester of L-arginine and an effective amount of an antioxidant are topically administered to the genitals of the female patient.

The Fossel et al. '713 patent discloses administration of L-arginine to produce enhanced blood flow in tissue which is said to cause beneficial effects such as warming cold tissue of the hands and feet, promoting hair growth, overcoming male erectile failure, etc.

Wallace '037 discloses administration of L-arginine for the treatment of cardiac pathologies and/or the treatment of erectile dysfunction.

Chobanian et al. '847 discloses the combination of angiotensin inhibitors and nitric oxide stimulators to slow and reverse the process of fibrosis in the body.

Duckett et al. '824 discloses the treatment of sexual dysfunction using a combination of L-arginine, ginseng and Zizyphi fructose in an orally administered dosage.

Wysor '002 discloses the enhancement of female sexual response by topical administration of a prostaglandin vasodilator.

The Combination of Chobanian et al. '847 with Fossel '713 or Wallace '037 Proposed in the Office Action is Improper and Should Be Withdrawn

Both Fossel et al. '713 and Wallace '037 disclose the administration of L-arginine for the treatment of male erectile failure or dysfunction. In contrast, Chobanian et al. '847 discloses the combination of angiotensin inhibitors and nitric oxide stimulators to slow and reverse the process of fibrosis in the body. The treatment of fibrosis by Chobanian et al. '847 represents non-analogous art with respect to both Fossel et al. '713 and Wallace '037 which disclose the treatment of male erectile dysfunction. There is no teaching, suggestion or motivation for combining Chobanian et al. '847 with either Fossel et al. '713 or Wallace '037 as proposed in the Office Action. Instead, the combination proposed in the Office Action represents the improper use of hindsight in which Appellants' claims have been used to piece together unrelated and nonanalogous prior art references. It is well established that such hindsight rejections are improper. Accordingly, since all of the 35 U.S.C. § 103(a) rejections are based upon a combination of Chobanian et al. '847 with Fossel '713 or Wallace '037, all of the rejections are improper and should be withdrawn.

The Combinations of References Proposed in the Office Action Fail to Render the Present Claims *Prima Facie* Obvious

Even if the references could properly be combined as proposed in the Office Action, such a combination fails to render the presently claimed invention *prima facie* obvious. The prior art of record does not teach or suggest the combination of topical administration to the genitals of a female patient an effective amount of esterified L-arginine comprising ethyl ester of L-arginine and an effective amount of an antioxidant. The applied references, in combination, fail to teach or suggest the

topical administration of a composition comprising esterified L-arginine to the genitals of a female patient. The applied references therefore fail to render the present claims *prima facie* obvious.

Appellants Have Demonstrated Unexpectedly Improved Results

Appellants have surprisingly and unexpectedly found that compositions comprising esterified L-arginine comprising ethyl ester of L-arginine and an antioxidant as presently claimed significantly enhance sexual response in females when topically applied, in comparison with similar compositions containing L-arginine.

The Rule 132 Declaration of Meir S. Sacks submitted with Appellants' July 28, 2004 Amendment supports Appellants' position that the presently claimed method provides unexpectedly improved results:

> The presence of esterified L-arginine comprising ethyl ester of L-arginine in the composition recited in this application significantly and unexpectedly improves sexual response in women who topically apply the composition. I conducted a study to demonstrate those facts. The study described below was conducted by me.
>
> Five women, each with various sexual dysfunctions, comprised the test group. Their dysfunctions ranged from the inability to produce any vaginal moisture (this woman having had laproscopic removal of the ovaries approximately three years prior to testing) to women with varying degrees of lack of orgasmic fulfillment. Results were graded on a 0 to 10 basis, as reported by the women, with 0 being no sexual response at all to 10 being an extremely powerful sexual response. Each woman was given compositions including: (1) a control (which was a PLO vehicle with no active ingredient); (2) a composition comprising the PLO vehicle with L-arginine and antioxidant (comprising a combination of ascorbic acid and ascorbic acid-6-palmitate in a 1:1 ratio); and (3) a composition comprising the PLO vehicle with esterified L-arginine (comprising the ethyl ester of L-arginine or a combination of the ethyl ester and the methyl ester of L-arginine) and antioxidant (comprising a combination of ascorbic acid and ascorbic acid-6-palmitate in a 1:1 ratio). The ratio of L-arginine or esterified L-arginine to antioxidant in compositions (2) and (3) was approximately 2:1. The compositions were formulated according to methods

commonly known to those skilled in the art for formulating liposomal solutions.

In a round of testing, the concentrations of L-arginine in composition (2) and L-arginine ethyl ester in composition (3) were approximately 25 milligrams. In response to the use of composition (3) containing the ethyl ester of L-arginine of the presently claimed invention, four of the five women reported increases in their sexual experience. The first woman, who was originally a 6, reported a response of almost 10 by using composition (3) containing the L-arginine ethyl ester. The woman with the inability to autolubricate went from 0 to a 10 in response to the L-arginine ethyl ester composition (3). The third woman went from a 2 to about a 6 based upon using the L-arginine ethyl ester composition (3). The fourth woman, who had previously rated her sexual experience at about 1, rated her experience, based upon using the L-arginine ethyl ester composition (3), at a 3. The fifth woman reported no significant differences between any of the categories.

None of the women reported a response to the control composition (1) or the L-arginine composition (2). When an enhanced sexual response was realized, it occurred with composition (3) comprising the esterified L-arginine. The results of the study are shown in the following table.

Sexual Response Score
(Scale of 1 to 10)

Subject No.	Baseline (No Treatment)	Composition 1 Control (Vehicle Alone)	Composition 2 Vehicle Plus L-Arginine and Antioxidant	Composition 3 Vehicle Plus Ethyl Ester of L-Arginine and Antioxidant
1	6	6	6	10
2	0	0	0	10
3	2	2	2	6
4	1	1	1	3
5	*	*	*	*

* Subject reported essentially no difference between categories.

This study demonstrates that the composition of the presently claimed invention comprising the ethyl ester of L-arginine produced unexpectedly improved results in comparison with both the composition comprising no active ingredient and the composition comprising L-arginine. (Sacks Declaration, Paragraphs 4-8)

The Sacks Declaration makes clear that the same five women tested the control composition, then the L-arginine plus antioxidant composition, and then the ethyl ester of L-arginine plus antioxidant composition. None of the women reported a response to the control composition or the L-arginine plus antioxidant composition, however, four of the women reported enhanced sexual response with the esterified L-arginine plus antioxidant composition corresponding to the presently claimed invention.

The Examiner states that he is unable to determine the significance of the results provided in the Sacks Declaration since:

> 1) so statistical evaluation was done; 2) no data regarding the age and the menstrual cycle time are provided since these determine the sexual responses by women; 3) there are no controls using L-arginine or ethyl ester of arginine or the antioxidants by themselves.

According to the Examiner, such an evaluation is essential since both arginine and the antioxidants by themselves have some effect on sexual activity as evident from the applied references. The Examiner points out that Appellants find no response at all for a combination of L-arginine and antioxidant in five women tested. The Examiner then poses the question: If that were to be the case, how can one be sure that any antioxidant would work well with even the ethyl ester of arginine?

It is submitted that the Sacks Declaration adequately demonstrates that a composition comprising esterified ethyl ester of L-arginine plus an antioxidant according to an embodiment of the claimed invention (Composition 3) produces unexpectedly improved results over a composition comprising L-arginine plus the same antioxidant (Composition 2), as well as a control (Composition 1). Contrary to the position taken by the Examiner, the Sacks Declaration compares, head-to-head, a composition representing the combination of references proposed by the Examiner (Composition 2 comprising L-arginine and an antioxidant) and a composition representing the presently claimed invention (Composition 3 comprising ethyl ester of L-arginine plus the same antioxidant).

The Sacks Declaration demonstrates that a composition of the presently claimed invention comprising ethyl ester of L-arginine produces unexpectedly improved results when applied to the genitals of the same female subjects in

comparison with a similar composition comprising L-arginine instead of the ethyl ester of L-arginine. As described in detail in the Sacks Declaration, application of a composition to the genitals of female subjects in accordance with the present invention resulted in significantly enhanced sexual responses. The Sacks Declaration further demonstrates that a composition of the presently claimed invention comprising ethyl ester of L-arginine and antioxidant produces unexpectedly improved results when applied to the genitals of female subjects in comparison with a control composition comprising no active ingredient. Appellants have therefore adequately demonstrated unexpectedly improved results achieved in accordance with the presently claimed method.

SUMMARY

For all of the reasons given above, Appellants respectfully submit that the rejections of Claims 13, 18, 19 and 21-25 under 35 U.S.C. § 103(a) are improper and should be reversed. It is respectfully requested that the case is in condition for allowance and, as such, that the case be remanded to the Examiner for the appropriate action.

Respectfully submitted,

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APPENDIX

13. A method for treating sexual dysfunction in a female patient comprising topically administering to the genitals of said patient an effective amount of esterified L-arginine comprising ethyl ester of L-arginine and an effective amount of an antioxidant.

18. The method of Claim 13, wherein the antioxidant is ascorbic acid or derivatives thereof.

19. The method of Claim 18, wherein said antioxidant is a combination of ascorbic acid and ascorbic acid palmitate.

21. The method of Claim 13, wherein said esterified L-arginine and said antioxidant are administered concurrently in the same composition.

22. The method of Claim 21, wherein said composition is in the form of a gel, ointment, foam, spray, cream, salve, lotion, liquid, emulsion or liposomal suspension.

23. The method of Claim 13, wherein said effective amounts are those amounts necessary to cause the desired level of blood flow to erectile tissue while minimizing peroxynitrite levels.

24. The method of Claim 13, wherein said esterified L-arginine and said antioxidant are applied to the clitoral hood.

25. The method of Claim 13, wherein said treatment results in enhancement of sexual pleasure.